

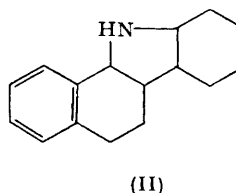
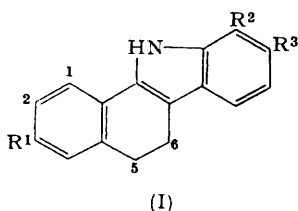
1141. Quasi-steroidal Heterocycles. Part IV.¹
5,6-Dihydrobenzo[*a*]carbazoles and Indolo[3,2-*c*]quinolines.

By P. E. CROSS and EMRYS R. H. JONES.

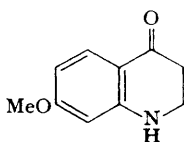
The synthesis is described of the nitrogen heterocyclic skeletons named in the title, with oxygen functions at positions corresponding to 3 and 17 in the steroid nucleus.

THE known² 5,6-dihydrobenzo[*a*]carbazole ring system (I), when furnished with oxygen functions at positions 3 and 10 (or 9), provides a tetracyclic structure in which these functions are in approximately the same spatial relationship as are those at positions 3 and 17 of the steroid nucleus. We have prepared from 6-methoxy-1-tetralone, using the Fischer indole synthesis on the appropriately substituted phenylhydrazone, two such compounds, (I; R¹ = R² = OMe, R³ = H) and (I; R¹ = R³ = OMe, R² = H).

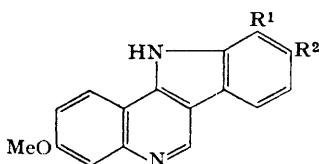
Birch reduction, using lithium in ammonia with *t*-butyl alcohol as proton source, gave from (I; R¹ = R³ = OMe, R² = H) a product which, from its infrared spectrum (ν_{\max} . 1668, 1618 cm.⁻¹, no benzene-ring bands), appeared to be the bis(dihydro)-derivative in which both benzene rings had been reduced (pyrrole rings are known³ to be resistant to Birch reduction). Hydrolysis of this initial product with methanolic oxalic acid gave a dark, intractable material. The parent 5,6-dihydrobenzo[*a*]carbazole (I; R¹ = R² = R³ = H), used as a model compound, was unaffected by stannous chloride; catalytic reduction using hydrogen and platinum in acetic acid gave the decahydro-derivative (II), shown to be an alkylbenzene rather than an aniline derivative by its ultraviolet spectrum and with a ratio of aliphatic to aromatic protons of 4:1 according to its n.m.r. spectrum (see Experimental section).



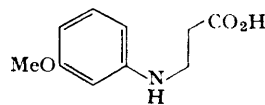
The analogous indoloquinolines, (IV; R¹ = R² = H), (IV; R¹ = H, R² = OMe), and (IV; R¹ = OMe, R² = H), were prepared in a similar way from the tetrahydro-oxoquinoline (III). In the latter, the presence of two electron-releasing groups causes depression of carbonyl reactivity, and the required phenylhydrazones could not be isolated, although a 2,4-dinitrophenylhydrazone was formed. However, when the ketone (III) and the appropriate phenylhydrazine were brought into reaction under indolizing conditions, the indoloquinolines (IV) were obtained. Atmospheric oxidation of the dihydroquinoline, which must be the



(III)



(IV)



(V)

¹ Part III, P. E. Cross and Emrys R. H. Jones, preceding Paper.

² C. U. Rogers and B. B. Corson, *J. Amer. Chem. Soc.*, 1947, **69**, 2910, and references therein.

³ S. O'Brien and D. C. C. Smith, *J.*, 1960, 4609.

initial product from the Fischer indole reaction with ketones such as (III), to the fully aromatic type (IV) is well known,⁴ as is a similar dehydrogenation in related indoles derived from *N*-substituted tetrahydroquinolones.⁵

The ketone (III) was previously available by a six-stage synthesis in low yield.⁶ The use of a recent method⁷ involving polyphosphoric acid cyclisation of the unprotected amino-acid (V) gave a practical three-stage synthesis of this ketone.

EXPERIMENTAL

Infrared spectra were obtained in Nujol using a Perkin-Elmer Infracord 137, ultraviolet spectra in 0.001% methanolic solution using a Perkin-Elmer 137, and n.m.r. spectra in a Varian A60 spectrometer at 60 Mc./sec. using tetramethylsilane as an internal standard ($\tau = 10.00$). Solvent extracts were dried over magnesium sulphate.

Preparation of the Benzo[a]carbazoles.—(a) 6-Methoxy-1-tetralone⁸ (1.0 g.), *o*-methoxyphenylhydrazine (1 ml.), acetic acid (1 ml.), and ethanol (10 ml.) were boiled under reflux for 4 hr. The mixture was cooled and the crystalline product recrystallised from ethanol, to give 6-methoxy-1-tetralone *o*-methoxyphenylhydrazone (1.1 g.), m. p. 96—98°. Further crystallisation raised the m. p. to 98—100° (Found: C, 73.4; H, 7.1; N, 9.4. C₁₈H₂₀N₂O₂ requires C, 73.0; H, 6.8; N, 9.5%). Repetition of this experiment on 10 g. of 6-methoxy-1-tetralone gave 12.6 g. of hydrazone, m. p. 97—99°. The hydrazone (9.0 g.), concentrated hydrochloric acid (5.3 ml.), and ethanol (100 ml.) were boiled under reflux for 5 hr. The mixture was filtered from ammonium chloride, evaporated to dryness, and the residue chromatographed on neutral alumina (200 g.) in 10% ethyl acetate-benzene, to give 5.9 g. of product, m. p. 102—106°. Recrystallisation from methanol gave 5,6-dihydro-3,10-dimethoxy-11H-benzo[a]carbazole (I; R¹ = R² = OMe, R³ = H) (2.9 g.), m. p. 116—118° (Found: C, 77.2; H, 6.0; N, 5.0. C₁₈H₁₇NO₂ requires C, 77.4; H, 6.1; N, 5.0%), ν_{\max} 815m, 781s, 737s cm.⁻¹.

The n.m.r. spectrum (CCl₄) shows two singlet CH₃O peaks (6.02, 6.23 τ), six aromatic protons (2.8—3.5 τ), and four aliphatic protons as a singlet (7.05 τ). The n.m.r. spectrum of 5,6-dihydrobenzo[a]carbazole² (CCl₄) also exhibits a singlet corresponding to four protons at 7.00 τ ; that of 5,6-dihydro-3-methoxybenzo[a]carbazole⁹ (CCl₄) shows a four-proton singlet at 7.03 τ .

(b) A solution of 6-methoxy-1-tetralone (4.4 g.) in ethanol (50 ml.) was added during 35 min. to one containing *m*-methoxyphenylhydrazine (3.45 g.) and concentrated hydrochloric acid (4.3 ml.) in ethanol (75 ml.) at the boil. After a further 5 hours' boiling, hot water (150 ml.) was added and the solution was cooled. The crystalline product was recrystallised from ethanol, to give 5,6-dihydro-3,9-dimethoxy-11H-benzo[a]carbazole (I; R¹ = R³ = OMe, R² = H) (2.2 g.), m. p. 200—202°; second crop (1.2 g.), m. p. 196—198° (Found: C, 77.3; H, 6.0; N, 5.2%), ν_{\max} 830m, 810s, no band between 810 and 730 cm.⁻¹. The n.m.r. spectrum (CDCl₃) shows two methoxyl peaks (6.17, 6.20 τ), six aromatic protons (2.5—3.2 τ), and a singlet (7.05 τ) corresponding to four aliphatic protons. 5,6-Dihydro-10-methoxy-11H-benzo[a]carbazole, prepared in a similar manner, chromatographed on neutral alumina in benzene, and crystallised from light petroleum (b. p. 60—80°), had m. p. 98—100° (2.3 g. from 4.0 g. of 1-tetralone) (Found: C, 81.9; H, 6.1; N, 5.4. C₁₇H₁₅NO requires C, 81.9; H, 6.0; N, 5.6%). The n.m.r. spectrum (CCl₄) shows a methoxyl peak (6.17 τ) and a four-proton singlet (7.09 τ).

Birch Reduction of 5,6-Dihydro-3,9-dimethoxy-11H-benzo[a]carbazole.—Lithium (1.0 g.) was added in small pieces during 30 min. to a stirred solution of the carbazole (1.0 g.) in redistilled liquid ammonia (25 ml.), tetrahydrofuran (12 ml.), and *t*-butyl alcohol (12 ml.). The mixture was then stirred for 3 hr., methanol was added to discharge the blue colour, excess ammonia was allowed to evaporate, water was added, and the solution was concentrated *in vacuo*. The crude bis(dihydro)-compound (1.0 g.) was collected, ν_{\max} 1668, 1618, with no bands at 1600, 1500 cm.⁻¹. It was dissolved in methanol (100 ml.) containing oxalic acid dihydrate (1.0 g.). After 2 hr. at room temperature, the solution was concentrated, water was added, and the product extracted into ethyl acetate. The extract was washed with aqueous sodium carbonate and water, dried, and evaporated, to give a dark, amorphous material from which no crystalline derivatives could be obtained.

⁴ G. R. Clemo and W. H. Perkin, jun. *J.*, 1924, **125**, 1608.

⁵ F. G. Mann, *J.*, 1949, 2816, and succeeding Papers in this Series.

⁶ J. T. Brauholtz and F. G. Mann, *J.*, 1957, 4166.

⁷ J. Koo, *J. Org. Chem.*, 1963, **28**, 1134.

⁸ G. Stork, *J. Amer. Chem. Soc.*, 1947, **69**, 576.

⁹ Ng. Ph. Buu-Hoi, Ng. Hoàn, Ng. H. Khói, and Ng. D. Xuong, *J. Org. Chem.*, 1950, **15**, 962.

Catalytic Reduction of 5,6-Dihydro-11H-benzo[a]carbazole.—No reduction took place when this compound was dissolved in aqueous ethanol (with or without added hydrochloric acid) and shaken under hydrogen (1 atm.) at room temperature, using a 5% platinum-, rhodium-, or ruthenium-carbon catalyst. The carbazole (0.50 g.) was dissolved in acetic acid (15 ml.), Adams catalyst (20 mg.) was added, and the mixture was hydrogenated at 50° for 12 hr. under 100 atm. hydrogen. The mixture was filtered from catalyst and evaporated to dryness, to give a residual oil. Thin-layer chromatography on alumina in ethyl acetate showed a single spot (R_F 0.71). Addition of ethereal oxalic acid gave a precipitate (310 mg., m. p. 206—208° with effervescence) which, after recrystallisation from ethanol, gave 6,6a,6b,7,8,9,10,10a,11,11a-decahydro-5H-benzo[a]carbazole oxalate hydrate, m. p. 213° (effervescence) (Found: C, 64.8; H, 7.6; N, 4.2. $C_{18}H_{23}NO_4 \cdot H_2O$ requires C, 64.5; H, 7.5; N, 4.2%), λ_{max} . 209 (ϵ 16,300) and a complex band centred at 265 $m\mu$ (ϵ 1000). The n.m.r. spectrum (trifluoroacetic acid) shows a ratio of aliphatic to aromatic protons of 4:1, the aromatic protons giving rise to a single peak at 3.09 τ .

Attempted reduction of 5,6-dihydrobenzo[a]carbazole with stannous chloride in boiling ethanol containing concentrated hydrochloric acid gave only starting material.

1,2,3,4-Tetrahydro-7-methoxy-4-oxoquinoline.—Crude *N-m*-methoxyphenyl- β -alanine (38 g.) was added to polyphosphoric acid (B.D.H., about 80% P_2O_5 ; 450 ml.) at 85°, with stirring. The internal temperature was raised to 95° and maintained at 95—100° for 15 min. The mixture was allowed to cool somewhat, poured on ice and 30% aqueous sodium hydroxide, and extracted with ethyl acetate. Evaporation of the dried extract gave the yellow product, m. p. 135—137° (from methanol) (lit.,⁶ 139°) (11 g., 32%). Thin-layer chromatography on alumina in 10% ethyl acetate-benzene showed a single spot, R_F 0.45, ν_{max} . 3370, 1645, 821, 800 cm^{-1} .

The *N-m*-methoxyphenyl- β -alanine used as starting material was prepared according to the method given by Johnson *et al.*¹⁰ for the unsubstituted *N*-phenyl- β -alanine ethyl ester, followed by hydrolysis of the ester. The ester (40 g.) was boiled under reflux for 3 hr. with 15% aqueous sodium hydroxide (200 ml.) and ethanol (30 ml.). The cooled mixture was extracted with ether to remove unchanged ester, then the aqueous layer was acidified with acetic acid, extracted with benzene, and the dried extract evaporated to give the required *N-m*-methoxyphenyl- β -alanine as a syrup (30—40%). The oxalate crystallised from ethanol-light petroleum (b. p. 60—80°), m. p. 136—138° (Found: C, 54.8; H, 5.8; N, 5.8. $C_{10}H_{13}NO_3 \cdot \frac{1}{2}C_2H_2O_4$ requires C, 55.0; H, 5.8; N, 5.8%).

Indolo[3,2-c]quinolines.—1,2,3,4-Tetrahydro-7-methoxy-4-oxoquinoline (2.40 g.), *m*-methoxyphenylhydrazine (2.10 g.), ethanol (25 ml.), and concentrated hydrochloric acid (6 ml.) were boiled under reflux for 18 hr. The mixture was cooled, and the crude product which separated was crystallised from methanol to give 3,9-dimethoxy-11H-indolo[3,2-c]quinoline hydrochloride (IV; $R^1 = H$, $R^2 = OMe$), m. p. 308—309° (1.40 g., 32%) (Found: C, 64.4; H, 4.9; N, 9.2. $C_{17}H_{14}N_2O_2 \cdot HCl$ requires C, 64.8; H, 4.8; N, 8.9%), λ_{max} . 234 (ϵ 39,000), 253 (36,800), 280 (47,800), 294 (34,900), 308 (20,400), 317 (infl., 15,100), and 340 $m\mu$ (5700).

3,10-Dimethoxy-11H-indolo[3,2-c]quinoline (IV; $R^1 = OMe$, $R^2 = H$) *Hydrochloride Hemihydrate.*—Prepared in a similar way and in similar yield, this compound had m. p. 280—282° (Found: C, 62.8; H, 5.0; Cl, 11.0; N, 8.9. $C_{17}H_{14}N_2O_2 \cdot HCl \cdot \frac{1}{2}H_2O$ requires C, 63.1; H, 5.0; Cl, 11.3; N, 8.7%), λ_{max} . 241 (ϵ 52,400), 270 (infl., 37,500), 278 (57,000), 290 (infl. 20,000), 307 (infl. 9700), and 328 $m\mu$ (infl. 7100).

3-Methoxy-11H-indolo[3,2-c]quinoline (IV; $R^1 = R^2 = H$) *Hydrochloride Dihydrate.*—This compound had m. p. 282—284° (Found: C, 60.0; H, 5.2; Cl, 11.4; N, 9.0. $C_{16}H_{12}N_2O \cdot HCl \cdot 2H_2O$ requires C, 60.0; H, 5.3; Cl, 11.1; N, 8.7%), λ_{max} . 236 (ϵ 33,200), 245 (infl. 27,200), 270 (infl. 31,800), 277 (56,400), 292 (infl. 20,000), 302 (13,900), and 312 $m\mu$ (8600).

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¹⁰ W. S. Johnson, E. L. Woroch, and B. G. Buell, *J. Amer. Chem. Soc.*, 1949, **71**, 1901.